6. (Amended) The composition of claim 1, wherein the desialyated glycoprotein-α 1 is coupled to the liposome by an avidin-biotin or thiol-maleamide linkages.

8. (Amended) A method for inhibiting the proliferation of liver cancer comprising the steps of:

(a) administering to a subject in need of such therapy an effective amount of a composition containing doxorubicin encapsulated in desialyated glycoprotein-α 1 coupled to a liposome; and

(b) delaying a cell division of cells.

Please add the following new claim 9.

9. (New) A composition for the targeted delivery of a therapeutic agent to a tissue expressing asialoglycoprotein receptors comprising an effective amount of a doxorubicin encapsulated in a liposome coupled to desialyated glycoprotein-α 1 by an avidin-biotin.

REMARKS

Entry of the foregoing amendment and reconsideration in light of the following remarks are respectfully requested. New Claim 9 has been added and presented for consideration. No new matter has been introduced.

Rejection under §112, 2nd ¶

Claims 3, 4, 6 and 8 stand rejected under 35 USC §112, 2nd ¶, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention.

The office action states Claim 3 is indefinite since it is unclear how cDNA "encodes" a ribozyme or an antisense DNA. Further, the office action states that Claim 4 is indefinite since it is an improper Markush claim and Claim 6 contains a typographical error. Finally, the office action states Claim 8 is indefinite for failing to specify a final step of the method which related

back to the preamble. Claims 3, 4, 6 and 8 have been amended and the rejection is now deemed moot.

In view of the foregoing amendment and comments, Applicants respectfully request reconsideration and withdrawal of the §112, 2nd ¶ rejection.

Rejection under §103 (a)

The office states Claims 1-8 stand rejected under 35 USC §103(a) as being unpatentable over Allen et al., Perez-Solar et al., Pratt et al., Martin, Hortobagyi, Menezes et al., Neitchev et al., and Mayer et al. This rejection is traversed on reasons provided below.

The office action relies on Allen et al. for the teaching of targeted liposomal drug delivery. Allen et al., neither teach nor suggest desialyated glycoprotein-alpha-1. More specifically, Allen et al., neither teach nor suggest a cytotoxic drug such as doxorubicin encapsulated in a liposome coupled to desialyated glycoprotein α 1.

Similarly, Hortobagyi, Martin, and Menezes et al. neither teach nor suggest coupling of desialyated glycoprotein-α 1. The office action further relies on Hortobagyi, Martin, Menezes, Pratt et al., and Mayer et al. for its suggestion of liposomal doxorubicin compositions. In contrast, Applicants' invention must be considered as a whole rather than piecemeal. Applicants invention is directed to compositions comprising an effective amount of a therapeutic agent encapsulated in a liposome coupled to a desialyated glycoprotein.

In addition, the office action relies on two references to teach the advantage of dose-limiting cardiotoxicity relative to daunorubicin or doxorubicin (Pratt et al.) and doxorubicin (Mayer et al.). Again, there is no mention made in Pratt et al. or Mayer et al. regarding compositions comprising an effective amount of a therapeutic agent encapsulated in a liposome coupled to a desialyated glycoprotein. Applicant draws the Examiner's attention to Figure 6 of the present application, which shows the effect of doxorubicin on myocardial injury and Applicants' discovery that anti-tumor activity of dox-liposomes was greatly enhanced when the liposomes were conjugated with desialo-A α G, such that anti-tumor effect became comparable to that of free dox.

Next, the office action relies on Perez-Solar et al. to teach "the potential advantages of liposome-encapsulated doxorubicin are a reduced cardiotoxicity as a result of lower cardiac drug levels and an increased activity against tumors that infiltrate the liver and spleen." Nonetheless, Perez-Solar et al., at page 4260, teach away from the present invention in that "evaluation of liposome doxorubicin was, however, delayed because of formulation problems that still remain unresolved. Furthermore, Perez-Solar et al., state at page 4265, 2nd full paragraph that "[i]t is difficult to predict with certainty whether these advantageous properties will be preserved in the new liposome formulations developed or new compounds synthesized".

Applicants note that Claims 1-8 were not rejected in the office action under §103(a) as being unpatentable over Park et al. Nonetheless, the office action relies upon Park et al. for the teaching of the ASGPR system and motivation of using agents which bind the ASGPR for targeted drug delivery. Applicants therefore provide the following comments. No mention is made in Park et al. to α-acid glycoprotein. Park et al. state on page 307 [t]he FACS data shows that even within the hepatic cell lines the expression level of ASGPR greatly differs. Park et al. neither teach nor suggest compositions comprising an effective amount of a therapeutic agent encapsulated in a liposome coupled to a desialyated glycoprotein and, more specifically, doxorubicin encapsulated and the like.

Finally, the office action relies on Neitchev et al. for its limited teaching of liposomes having alpha-1glycoprotein. Nonetheless, Neitchev et al. neither teach nor suggest use of liposomes to target delivery of therapeutic compositions and specifically to the liver. Similarly, Neitchev et al. neither teach nor suggest the combination of an effective amount of an agent encapsulated in a liposome coupled to desialyated glycoprotein α 1 and, more specifically, doxorubicin encapsulated and the like.

Applicants' present invention and coupling of desialyated glycoprotein-α 1 to liposomes further improves the selectivity and enhances the efficacy of doxorubicin as supported in both tissue distribution and *in vivo* studies. Surprisingly, the anti-tumor activity of dox-liposomes was greatly enhanced when the liposomes were conjugated with desialo-A α G in the present invention.

Absent some suggestion in the relied on references to combine, the office action uses impermissible highsight to reconstruct the relied on references to arrive at Applicants' invention. Applicants therefore respectfully request the rejection of Claims 1-8 under §103(a) be reconsidered and withdrawn.

CONCLUSION

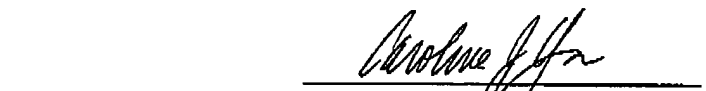
Applicants respectfully request reconsideration and allowance of all claims. If the Examiner has any questions or other correspondence regarding this application, Applicants request that Examiner contact the Applicants' attorney at the change of correspondence at the below-listed telephone number and overseas address. An associate power of attorney and one month petition for extension of time / fee accompany this response. It is believed no additional fees are required to be paid at this time, however, in the event any other fee is due, authorization to charge deposit account no. 13-0480 (Attorney Docket No. 32144183-001336) is provided.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned **VERSION WITH MARKINGS TO SHOW CHANGES MADE**.

Favorable action is respectfully requested.

Respectfully submitted,

BAKER & McKENZIE



YUN, Caroline Joo
Reg. No. 34,952

March 6, 2002
Caroline J. Yun
BAKER & McKENZIE
14th Floor, Hutchison House
10 Harcourt Road, Central, Hong Kong
(852) 2846 1800 (general)
(852) 2846 2453 (direct)
(852) 2845 0476 (facsimile)
caroline.j.yun@bakernet.com (email)

VERSION WITH MARKINGS TO SHOW CHANGES MADE

The amendments to the claims are illustrated below with boldfaced underlined text representing what has been added and boldfaced bracketed text representing what has been deleted.

IN THE CLAIMS

3. (Amended) The composition of claim 2, wherein the polynucleotide is **selected from the group consisting of cDNA** encoding a therapeutic protein, a ribozyme, and antisense DNA.

4. (Amended) The composition of claim 1, wherein the therapeutic agent is selected from the group consisting of a cytotoxic drugs**[,] and** a protein.

6. (Amended) The composition of claim 1, wherein the desialyated glycoprotein-α 1 is coupled to the liposome by an avidin-biotin or thiol-maleamide linkages.

8. (Amended) A method for inhibiting the proliferation of liver cancer **[by] comprising the steps of:**

(a) administering to a subject in need of such therapy an effective amount of a composition containing doxorubicin encapsulated in desialyated glycoprotein-α 1**; and**

(b) delaying a cell division of cells.

9. (New) **A composition for the targeted delivery of a therapeutic agent to a tissue expressing asialoglycoprotein receptors comprising an effective amount of a doxorubicin encapsulated in a liposome coupled to desialyated glycoprotein-α 1 by an avidin-biotin.**